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ADDENDUM FOR CARBON TETRACHLORIDE

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OFFICE OF WATER REGULATIONS
AND STANDARDS

Prepared by

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Cincinnati, OH 45268

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PREFACE

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. The first draft of this addendum was prepared by Syracuse Research Corporation under contract no. 68-C8-0004.

TABLE OF CONTENTS

	Page
INTRODUCTION	1
REVIEW OF NEW DATA	4
Toxicologic/Carcinogenic Effects	4
Bioconcentration Factor (BCF)	7
QUANTIFICATION OF EFFECTS	8
EXISTING STANDARDS AND CRITERIA	10
REFERENCES	12

LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
BUN	Blood urea nitrogen
CRAVE	Carcinogen Risk Assessment Verification Endeavor
DWEL	Drinking water equivalent level
GPT	Glutamic pyruvic transaminase
HA	Health advisory
MCL	Maximum contaminant level
MCLG	Maximum contaminant level goal
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
OCT	Ornithine-carbamyl transferase
ppb	Parts per billion
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity
SDH	Sorbital dehydrogenase
SNARL	Suggested no-adverse response level
TLV	Threshold limit value
TWA	Time-weighted average

INTRODUCTION

Under Section 304(a)(1) of the Clean Water Act of 1977 as amended in 1987, the U.S. EPA is required to publish criteria for water quality accurately reflecting the latest scientific knowledge regarding the effects on health and welfare that may occur from the presence of pollutants in any body of water, including groundwater. In accordance with the 1977 act, Ambient Water Quality Criteria Documents (AWQCDs) were developed in 1980 for 65 toxic pollutants or classes of pollutants listed under Section 307(a)(1).

These addenda are intended to serve as an update of the original AWQCDs. The addenda provide the Agency with the latest scientific assessments of potential health hazards associated with these pollutants and serve as guidelines for modifying the current (1980) AWQCDs.

The human health criteria in these addenda are based on Agency verified risk assessment values when available. These values consist of reference doses (RfD) for those chemicals believed to be systemic toxicants (i.e., do not induce cancer) and cancer risk factors for those thought likely to cause cancer in humans The verification process consists of a review and consensus of risk assessment values provided by an Agency workgroup consisting of scientists from each of the major Agency offices. Assessments for noncarcinogens are verified by the RfD workgroup and those for carcinogens are verified by the Carcinogen Risk Assessment Ver' .cation Endeavor (CRAVE) workgroup. If such values are not available, .e criteria are based on the most recent Agency health assessment. In the absence of any appropriate Agency value, RfD values or cancer risk factors are derived by current Agency methods if adequate new data are available, and criteria are recommended based on the proposed RfD or risk factor.

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is derived by dividing a NOAEL or LOAEL for subchronic or chronic exposure by standard uncertainty factor(s) times an additional uncertainty factor:

$$RfD = \frac{\text{NOAEL or LOAEL}}{UF(s) \times UF}$$

The standard uncertainty factors are applied to reflect the various types of data used to estimate RfDs. An uncertainty factor of 10 is used to account for variations in human sensitivity when extrapolating from valid human studies involving long-term exposure of average, healthy subjects. An additional 10-fold factor is used for each of the following: to extrapolate from long-term animal studies to the case of humans, to extrapolate from subchronic animal studies to chronic exposure, and to extrapolate from a LOAEL to a NOAEL. An additional uncertainty factor of >0-10 may be applied to reflect professional assessment of the uncertainties of the study and data base not explicitly addressed by the standard uncertainty factors (i.e., completeness of the overall data base). The default value for the additional uncertainty factor is 1.

In assessing the carcinogenic potential of a chemical, the U.S. EPA classifies the chemical into one of the following groups according to the degree of evidence in epidemiological studies and animal studies: Group A - Human Carcinogen; Group B - Probable Human Carcinogen [limited evidence in humans with or without sufficient evidence in animals (Group B1) or inadequate evidence in humans with sufficient evidence in animals (Group B2)]; Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); Group D - Not Classifiable as to

Human Carcinogenicity (inadequate or no evidence); Group E - Evidence of Noncarcinogenicity for Humans. Quantitative carcinogenic risk assessments are performed for chemicals in Groups A and B, and on a case-by-case basis for chemicals in Group C. Upper-bound cancer unit risks (slope values) are estimated through the use of mathematical extrapolation models. Most commonly for animal data, the linearized multistage model with a 95% upper confidence limit is used to provide a low-dose estimate of cancer risk. The cancer risk is characterized as an upper-limit estimate (i.e., the true risk to humans, while not identifiable, is not likely to exceed the upper-limit estimate and in fact may be lower). Alternative risk models to the multistage model, such as the one-hit, Weibull, Logit or Probit model, are available and may be used when the evidence indicates that they may be more appropriate. In the absence of such evidence, the Agency recommends the linearized multistage model to provide consistency of approach and an upper-bound on the potential carcinogenic risk. In the case where human data are used for quantitative risk assessment, an upper-bound estimate rather than a 95% upper-bound estimate is used when low-dose linearity is assumed.

In the development of this Addendum to the AWQCD on carbon tetrachloride, recent Agency assessments have been consulted. A computerized literature search was conducted to cover studies published more recently than the latest Agency assessment (i.e., published in 1986 to 1988). New key studies have been evaluated.

REVIEW OF NEW DATA

Toxicologic/Carcinogenic Effects

The 1980 ambient water quality criteria were based on the carcinogenicity of carbon tetrachloride; dose-response data for liver tumors in male mice treated with carbon tetrachloride by gavage (NCI, 1976a,b) were used for quantitative risk assessment (U.S. EPA, 1980). No new studies that would impact the carcinogenicity risk assessment were found in the primary literature or in Agency assessments published since 1980.

The verified slope factor (U.S. EPA, 1986) is based on data that were reviewed in U.S. EPA (1980) and on data regarding the induction of hepatocellular carcinomas by carbon tetrachloride in rats (NCI, 1976a,b, 1977) that were not reviewed in U.S. EPA (1980), but were reviewed in later assessments (U.S. EPA, 1984, 1985). Carbon tetrachloride was used as the positive control substance in the NCI bioassays for chloroform (NCI, 1976a), 1,1,1-trichloroethane (NCI, 1977) and trichloroethylene (NCI, 1976b). Osborne-Mendel rats (50/sex/exposure group; 100/sex/control group) were given carbon tetrachloride in corn oil by gavage 5 days/week for 78 weeks, followed by observation through 110 weeks (NCI, 1976a,b, 1977). The doses were 47 or 94 mg/kg for the males and 80 or 150 mg/kg for the females. There were both matched (n=20/sex) and pooled colony (n=77 males, 80 females) controls. At 110 weeks, only 7/50 males and 14/50 females survived the high-dose treatment, and only 14/50 males and 20/50 females survived the low-dose treatment compared with 26/100 males and 51/100 females in the control groups.

The incidence of hepatocellular carcinomas was increased in animals exposed to carbon tetrachloride compared with pooled colony controls.

However, the only statistically significant ($p<0.05$) increase in the incidence of hepatocellular carcinomas was in the low-dose female rats (4/49) compared with colony controls (0/98), but not to matched controls (no hepatocellular carcinomas; number at risk not provided). Absolute incidence of hepatic neoplasms was low (~5% in the animals exposed to carbon tetrachloride). The decreased incidence of carcinomas in the high-dose females (1/30) was attributed to early death. The incidence of other neoplasms was acknowledged but not quantified. The National Research Council used these data in estimating carcinogenic risks for carbon tetrachloride (NAS, 1978).

B6C3F1 mice were also studied in these experiments; the results in the male mice were used in the derivation of the 1980 criteria (U.S. EPA, 1980). Carbon tetrachloride (1250 or 2500 mg/kg bw) was given by oral gavage to B6C3F1 mice, 35 days of age (50/sex/group) 5 days/week for 78 weeks (NCI, 1976a,b, 1977). Hepatocellular carcinomas were seen in 96-100% of the treated mice of both sexes and doses, in contrast to only 1% (females) or 6% (males) of the colony pooled control mice.

New studies pertinent to derivation of an oral RfD for carbon tetrachloride were evaluated by U.S. EPA (1985). In the key study, Sprague-Dawley rats (males, 16/group) were given carbon tetrachloride (0, 1, 10, or 33 mg/kg/day) in corn oil by gavage, 5 days/week for 12 weeks (Bruckner et al., 1986). No apparent adverse effects were observed at the 1 mg/kg dose level. A dose of 10 mg/kg produced mild centrilobular vacuolization. The dose of 33 mg/kg produced marked hepatotoxicity. The effect of carbon tetrachloride on several serum parameters was examined. The administration of 1 mg/kg had no effect on OCT, GPT, SDH or BUN. At the 10 mg/kg dose level, there were no effects on OCT or GPT except for a slight increase in

GPT at the end of the 12-week period. There was a 2- to 3-fold increase over controls in SDH; however, this increase was not always sufficient to be statistically significant. At the 33 mg/kg dose level, substantial increases were observed in SDH, OCT and GPT levels. There was no evidence of necrosis, fibrosis or other serious degenerative changes at the lower doses. At the 33 mg/kg dosage level, there was a significant decrease from controls in body weight gain and a significant increase in the liver-to-body weight ratio, with extensive degenerative lesions including fibrosis, centrilobular vacuolization and leukocyte infiltration. No evidence of kidney damage was seen in any of the groups other than a slight increase in the kidney-to-body weight ratio in the 33 mg/kg dose group.

The RfD work group also considered two other studies that supported the verified RfD (Condie et al., 1986; Hayes et al., 1986). These were both studies of the effects of carbon tetrachloride administered in corn oil by gavage to CD-1 mice, which showed hepatocellular toxicity at doses similar to those given in the Bruckner et al. (1986) study.

Hayes et al. (1986) administered carbon tetrachloride (0, 12, 120, 540, or 1200 mg/kg) in corn oil by gavage to CD-1 mice (20/sex/group) for 90 days. The following parameters were evaluated: general appearance and signs of intoxication, behavioral changes, body weight, hematology, serum enzyme chemistries, organ weights and ratios, liver and kidney histology, urinalysis and mortality. There were significant changes in serum chemistry and liver histology, indicating dose-related hepatotoxicity in all treatment groups.

Condie et al. (1986) administered carbon tetrachloride to CD-1 mice (12/sex/group) at dose levels of 0, 1.2, 12 or 120 mg/kg in either corn oil or 1% Tween-60 aqueous emulsion 5 days/week for 12 weeks. Body weight, food

and water consumption, clinical blood chemistry levels and liver tissues were examined. When the corn oil was used, the NOAEL was lower (1.2 mg/kg) than when the Tween was used. The corn oil was also found to enhance the hepatotoxicity in the two higher dose groups, as indicated by selected serum enzyme levels. The major lesion with both vehicles was hepatocellular vacuolization.

Bioconcentration Factor (BCF)

Pertinent new information concerning the bioconcentration factor for carbon tetrachloride is undergoing Agency review. The BCF value of 18.75 determined in U.S. EPA (1980) will be used until this review is complete.

QUANTIFICATION OF EFFECTS

The current ambient water quality criteria for human health for carbon tetrachloride corresponding to lifetime increased cancer risk levels of 10^{-5}, 10^{-6} and 10^{-7} are 0.04, 0.40 and 4.0 µg/ℓ, respectively, for consumption of water and fish and shellfish, and 0.69, 6.94 and 69.4 µg/ℓ for consumption of fish and shellfish only. The values assume a 70 kg human body weight, a daily intake of 2 ℓ of water and 6.5 g fish and shellfish, and a BCF of 18.75. The potency factor of 0.08275/mg/kg/day was derived from an NCI (1976a,b) study in which male mice receiving carbon tetrachloride had increased numbers of liver tumors.

In the four studies chosen as the basis for the current Agency risk assessment, ingestion of carbon tetrachloride produced hepatocellular carcinomas in male and female animals of three species. In male and female rats, the unit risk factor was 3.1×10^{-7}/µg/ℓ (NCI, 1976a,b, 1977), in male and female mice, the unit risk factors were 9.4×10^{-6} (Edwards et al., 1942) and 1.8×10^{-6} (NCI, 1976a,b, 1977), and in male and female hamsters, the unit risk factor was 3.4×10^{-5} (Della Porta et al., 1961). The rat data from the NCI studies (1976a,b, 1977) were the only data that were not considered in the 1980 AWQCD (see previous section).

Because all four studies were considered deficient in some aspects and because the risk estimates from these four studies in different species and strains were relatively close (within 2 orders of magnitude), the U.S. EPA (1986) concluded that the best approach was to use the geometric mean of risk estimates from all four studies. The verified oral unit risk factor of 3.7×10^{-6}/µg/ℓ was calculated as the geometric mean of the unit risk factors from these four studies; the corresponding verified slope factor is

0.13/mg/kg/day (U.S. EPA, 1986). This verified oral slope factor is recommended as the basis for deriving new ambient water quality criteria.

Using the verified slope factor of 0.13/mg/kg/day and assuming 70 kg body weight and a daily intake of 2 ℓ of water and 6.5 g of fish and shellfish with a BCF of 18.75, the criteria for carbon tetrachloride in ambient water are as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (µg/ℓ)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 ℓ of drinking water and consumption of 6.5 g fish and shellfish	0	0.025	0.25	2.5	25
Consumption of fish and shellfish only	0	0.45	4.5	45	450

EXISTING STANDARDS AND CRITERIA

Although carbon tetrachloride is considered a carcinogen, a recent Agency assessment provides a verified oral RfD of 7×10^{-4} mg/kg/day (U.S. EPA, 1985). This RfD is based on the study by Bruckner et al. (1986), which showed liver damage in rats (see Review of New Data).

Carbon tetrachloride is classified as U.S. EPA Group B2, a probable human carcinogen (U.S. EPA, 1986), based on adequate evidence of carcinogenicity in three animal species..

The verified oral slope factor is 0.13/mg/kg/day (see previous section) and the verified drinking water unit risk factor is 3.7×10^{-6}/µg/ℓ (U.S. EPA, 1986).

The quantitative estimates of carcinogenic risk from inhalation exposure are listed in IRIS (U.S. EPA, 1986). The verified inhalation slope factor is 0.013/mg/kg/day.

The drinking water HAs (U.S. EPA, 1988) are all based on the liver toxicity study by Bruckner et al. (1986). The 1-day, 10-day and longer-term HAs for a child are 4, 0.16 and 0.071 mg/ℓ, respectively. The longer-term HA for an adult is 0.25 mg/ℓ. The DWEL is 0.02 mg/ℓ. No lifetime HA has been estimated, and U.S. EPA (1988) notes that carbon tetrachloride is considered to be a probable human carcinogen. The NAS (1980) recommended 1-day and 7-day SNARLs of 14 mg/ℓ and 2 mg/ℓ, respectively.

The odor perception threshold is 0.52 mg/ℓ (U.S. EPA, 1988).

The MCLG for drinking water is 0, based on its carcinogenicity, and the MCL is 5 ppb (U.S. EPA, 1988).

The proposed RQ is 10 pounds, based on potential carcinogenicity and U.S. EPA weight of evidence Group B2 (U.S. EPA, 1988).

The ACGIH (1987) adopted a TWA-TLV value for carbon tetrachloride of 5 ppm (~30 mg/m^3), with a skin notation and classification as a suspected human carcinogen (A2).

The OSHA (1985) 8-hour TWA is 10 ppm, and the acceptable ceiling concentration is 25 ppm. The acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift is 100 ppm for a maximum duration of 30 minutes.

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